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EXAMINER	
GODDARD, LAURA B	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/994,068	ARAKAWA ET AL.	
	Examiner	Art Unit	
	Laura B. Goddard, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *19 October 2006 and 21 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-56* is/are pending in the application.

4a) Of the above claim(s) *25-28,31-41 and 44-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-24,29,30,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 19, 2006 and August 21, 2006 have been entered.

Claims 19-24, 29, 30, 42, and 43 are currently under prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 24, 42, and 43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not

precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method for treating cancer characterized by overexpression of Her2 in a patient comprising administering an antibody that binds Her2 and indices apoptosis in Her overexpressing cells, wherein the antibody is produced by the hybridoma cell line ATCC No. HB 12078 (claim 24), wherein the antibody binds an epitope on Her2 which is recognized by a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078 and wherein the antibody is administered with a chemotherapeutic agent (claim 42), the method of claim 42 wherein the chemotherapeutic is cisplatin or 5-FU (claim 43).

The specification teaches apoptosis induced in cell culture by mAb74 (produced by hybridoma ATCC No. HB 12078), wherein the induction of apoptosis was an unexpected result (p. 4, lines 25-28).

One cannot extrapolate the disclosure of the specification to the scope of the claims because the specification does not provide examples or guidance for treating cancer in a patient comprising administering a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope, wherein the antibody induces apoptosis. Those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. The specification discloses that mAb74 (produced by hybridoma ATCC No. HB 12078) induced apoptosis in cell lines overexpressing Her2, however, one of skill in the art would not extrapolate the induction of apoptosis in cell culture to the treatment of cancer in a patient because of the lack of physiological, immunological, environmental properties present during *in vitro* testing.

Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex

conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Further, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. Drexler et al teach that only a few cell lines containing cells that resemble the in-vivo cancer cells have been established and even for the bona fide cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see abstract).

In re Brana 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) demonstrates requirements for enablement of a product for pharmaceutical use *in vivo*. The Applicants in *In re Brana* claimed a chemical compound capable of treating cancer, wherein the chemical compound was structurally similar to known compounds that have known *in vivo* use to treat tumors, and more importantly, the Applicant provided *in vivo* data that the claimed compound could treat tumors in mice, hence the claimed chemical compound was enabled for treating tumors *in vivo*. In the instant application, unlike in *In re Brana*, the antibody that binds to Her2 has an "unexpected" result of inducing apoptosis *in vitro*, and a search of the current art does not teach or enable a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope to treat cancer in a patient. Additionally, the instant application, unlike in *In re Brana*, does not provide *in vivo* data for the treatment of cancer using a monoclonal antibody produced by hybridoma cell line

ATCC No. HB 12078, or an antibody that binds to the same epitope. Hence, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Further, with regards to the "unexpected" effect of the antibody *in vitro*, and the unknown ability of the antibody to treat cancer *in vivo*, it is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

MPEP 2164.03 states: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art.

Accordingly, what is known in the art provides evidence as to the question of predictability. Given the surprising nature of the antibody *in vitro,* the lack of correlation between *in vitro* assays and *in vivo* treatment, the altered nature of cell lines as compared to their *in vivo* counterparts, one of skill in the art could not predictably treat Her2 overexpressing cancer in a patient comprising administering a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope as claimed.

Therefore, in view of the novel nature of the invention, what is unknown in the art because of the novel nature of the invention, the state of the art, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 19-21, 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Shepard et al (J of Clinical Immunology, 1991, 11:117-127).

The claims are drawn to a method for treating cancer characterized by overexpression of Her2 in a patient comprising administering an antibody or fragment thereof that binds Her2 and induces apoptosis in Her2 overexpressing cells (claim 19), wherein the antibody is monoclonal (claim 20), wherein the antibody is humanized (claim 21), the method of claim 19, wherein the antibody or fragment thereof is administered with a chemotherapeutic agent (claim 29), and wherein the chemotherapeutic agent is cisplatin (claim 30).

Shepard et al teach a method for treating cancer characterized by overexpression of Her2 comprising administering monoclonal antibody 4D5 that binds to Her2 (abstract; p. 122, col. 2 to p. 123, col. 1; Table IV). Shepard et al teach humanization of the antibody that will make it more suitable for chronic therapy (p. 126, col. 1). Shepard et al teach treating cancer using antibody 4D5 with cisplatin (p. 126, col. 1).

As evidenced by Le et al (Clinical Cancer Research, 2000, 6:260-270) monoclonal antibody 4D5 is known to induce apoptosis (p. 266, col. 2, last paragraph). As evidenced by Mohsin et al (J Clin Oncology, 2005; 23:2460-2468), trastuzumab, which is the humanized monoclonal antibody 4D5, induces apoptosis in breast cancer overexpressing Her2 (abstract; p. 2461, col. 1; Fig. 3; p. 2465, col. 1). As evidenced by Bussolati et al (British J of Cancer (2205, 92:1261-1267), trastuzumab consists of the antigen binding fragments of antibody 4D5 and is the humanized version of 4D5 (p. 1261, col. 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shepard et al (J of Clinical Immunology, 1991, 11:117-127) as applied to claim 19 above, and further in view of US Patent 5,001,225, Taylor, filed 12/8/1986, issued 3/19/1991.

The claim is drawn to the method of claim 19 wherein the antibody or fragment thereof is a Fab or Fab' fragment.

Shepard et al teach a method for treating cancer characterized by overexpression of Her2 comprising administering monoclonal antibody 4D5 that binds to Her2 as set forth above.

Shepard et al does not teach that the Her2 antibody, monoclonal antibody 4D5, is a fragment.

US Patent 5,001,225 teaches that Fab and $F(ab')_2$ fragments lack the Fc fragment of an antibody, clear more rapidly from circulation and have less nonspecific tissue binding than intact antibody (col 9, lines 22-25) and further teach that Fab, F(ab')2 fragments may be used as well as the intact antibody in methods of treatment (col 9, lines 26-32).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make and use Her2 antibody Fab or Fab' fragments in the method taught by Shepard et al because the antibody fragments would have less nonspecific tissue binding than intact antibody and would treat Her2 overexpressing cancer. One of ordinary skill in the art would have been motivated to substitute the Her2 antibody with antibody fragments in order to successfully and more efficiently localize antibodies to tumor cells for purposes of treating Her2 overexpressing cancer.

5. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shepard et al (J of Clinical Immunology, 1991, 11:117-127) as applied to claim 19 above, and further in view of Reichmann al (Nature, 1988, 332:323-327).

The claim is drawn to the method of claim 19, wherein the antibody is a human antibody.

Shepard et al teach a method for treating cancer characterized by overexpression of Her2 comprising administering monoclonal antibody 4D5 that binds to Her2 as set forth above. Shepard et al teach humanization of the antibody for clinical use in humans (p. 126, col. 1).

Shepard et al does not teach that the Her2 antibody is human.

Reichmann al teach that murine monoclonal antibodies comprise foreign immunoglobulin that can elicit an anti-globulin response which may interfere with therapy or cause allergic or immune complex hypersensitivity. Thus ideally human antibodies would be used (p. 323, col. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to use human Her2 antibodies in the method taught by Shepard et al in order to treat Her2 overexpressing cancer in patients more efficiently by avoiding the anti-globulin response to the foreign murine antibody that would inhibit antibody treatment. One of ordinary skill in the art would have been motivated to use human antibodies in the method taught by Shepard et al because they have advantages of avoiding the anti-globulin response to the foreign murine antibody that would inhibit antibody treatment and avoiding an allergic or immune complex hypersensitivity caused by the foreign antibody.

Relevant Arguments

Claim Rejections - 35 USC § 112

6. Applicants argue that the property of an antibody inducing apoptosis in cell culture would also function to induce apoptosis *in vivo*. Applicants argue that the specification teaches how to make and use an that binds Her2 and induces apoptosis in Her2 overexpressing cells without undue experimentation. For example the specification teaches this at Example 2 and 6. Applicants argue that obtaining monoclonal antibodies needed to practice the claimed invention would not require undue experimentation and that screening for antibodies with the desired characteristic of inducing apoptosis in Her2 overexpressing cells would not be undue (p. 3-5).

The argument has been considered but is not found persuasive because screening for antibodies in cell culture does not enable the claimed method for treating cancer. While screening for Her2 antibodies in cell culture that induce apoptosis may not be undue, practicing the claimed method of *treating cancer in a patient* would be undue experimentation for all of the reasons set forth above in the enablement rejection of section 5.

7. Applicants argue that the specification is enabling for using the screened antibodies in the method for treating Her2 overexpressing cancer because it teaches how to make a pharmaceutical composition comprising said antibodies and routes of administration (p. 5).

The argument has been considered but is not found persuasive because Applicants have not provided data enabling the antibodies for treating cancer *in vivo* and the art does not teach that the antibodies of the claim are enabled. The specification is not enabling for the reasons set forth above in the enablement rejection of section 5.

8. Applicants argue that the enablement of the claimed invention does not require that the prior art disclose the exact method, rather that it is only required that one skilled in the art using the teaching of the specification and the knowledge in the art be able to practice the claimed method without undue experimentation (p. 5-6).

The argument has been considered but is not found persuasive because Examiner is not requiring disclosure of the invention in the prior art to be enabled. Post-filing art teaching the claimed antibody treating cancer *in vivo* would be enabling for *in vivo* treatment. Or as stated in the enablement rejection of section 5 with regards to *In re Brana*, prior art disclosing and antibody that binds to the same epitope or shares the same structure and function and is enabled for treating cancer would enable the claimed antibody for treating cancer. However, neither the prior art nor post-filing art enable the claimed antibodies for treating cancer. The claimed method would require undue experimentation for the reasons set forth above in the enablement rejection of section 5.

9. Applicants enclosed several references (Feldmann et al, Weiner et al, Maini et al) and argue that these reference enable the claimed invention (p. 6).

The argument has been considered but is not found persuasive because each of the articles submitted do not teach or enable the treatment of Her2 overexpressing cancer in a patient comprising administering a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope, wherein the antibody induces apoptosis. Feldmann et al teach an anti-TNFα antibody used to treat rheumatoid arthritis, which is not related to Her2, cancer, or her2 antibodies. Maini et al teach an anti-TNFα antibody used to treat rheumatoid arthritis which is not related to Her2, cancer, or her2 antibodies. Weiner et al teach a bispecific antibody that binds CD3 on a T cell and a tumor antigen on a B cell to retarget T cells towards tumor

cells in an MHC independent manner, which is not related to Her2, cancer, or her2 antibodies. The articles do not teach or enable the treatment of Her2 overexpressing cancer in a patient comprising administering a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope, wherein the antibody induces apoptosis.

10. Applicants argue that the claimed method is enabled because of a post-filing journal article written in Japanese, Saski et al. Applicants submitted the abstract which was the only English translation of the article (p. 6). Applicants argue that the abstract teaches a chimeric Her2 antibody, CH401, that kills cancer cells by inducing apoptosis in Her2 overexpressing cells both *in vitro* and *in vivo*. Applicants assert that this abstract supports their extrapolation of *in vitro* results to *in vivo* results for the treatment of cancer.

The argument has been considered but is not found persuasive because there is insufficient evidentiary support from the English abstract to enable extrapolation of the *in vitro* results for a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope, to the *in vivo* treatment of cancer. The abstract teaches that a monoclonal Her2 antibody, CH401, was established and characterized in the laboratory. The abstract states: "CH401 is able to kill cancer cells overexpressing Her2 both *in vitro* and *in vivo*. The analysis of this tumor growth inhibition by CH401 made it clear that the cytotoxicity was induced by apoptosis. These results may suggest that CH401 has therapeutic potential for Her2

overexpressing cancers and this approach may be particularly valuable as a new type of cancer therapy." The abstract fails to disclose the *in vitro* and *in vivo* model used, data supporting cancer treatment, and the data supporting apoptosis. The abstract fails to teach the treatment of cancer comprising administering a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope, to the *in vivo* treatment of cancer. While the abstract suggests using antibody CH401 as a new type of cancer therapy, it does not enable the claimed invention, nor provide support for extrapolating *in vitro* assays to the treatment of cancer.

11. Applicants argue that the Voskoglou-Nomikos et al (Clinical Cancer Research, 2003, 9:4227-4239) article teaches that the list of 60 human cancer cell lines used in the screen and maintained by the National Cancer Institute enable the extrapolation of *in vitro* to *in vivo* cancer therapy because the reference teaches that the "*in vitro* cell line model was predictive for non-small cell lung cancer under the disease-oriented approach, for breast and ovarian cancers under the compound-oriented approach, and for all four tumor types together". Applicants also state that the reference teaches "...the *in vitro* cell line model was found to be predictive of Phase II clinical performance for NSCLC under the disease-oriented approach and in the case of all four tumor types together. Highly significant correlations were observed in all cases, except the colon cancer...". Applicants also state that the reference teaches "the work presented here argues for emphasis to be placed on *in vitro* cell lines (in the

context of the NCI Human Tumor Cell Line Screen) and appropriate panels of the human xenograft model."

The argument has been considered but is not found persuasive because Voskoglou-Nomikos et al teach clinical predictive value of the *in vitro* cell line for compounds or chemicals and does not teach the predictive value of cell culture studies for Her2 antibodies and the treatment of Her2 overexpressing cancer. Voskoglou-Nomikos et al teach that the cell line model was predictive for non-small cell lung cancer under the "disease-oriented approach", which does not enable the extrapolation of *in vitro* data to the enablement of treating cancer comprising administering a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope. Voskoglou-Nomikos et al teach that the *in vitro* cell line model was predictive for breast and ovarian cancers under the compound-oriented approach, however, this does not enable the extrapolation of *in vitro* data to the enablement of treating cancer comprising administering a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope because the specification does not teach a "compound-oriented approach", nor is the claimed invention related to compounds as in the context of the reference. Voskoglou-Nomikos et al does not teach the predictable extrapolation of *in vitro* data for Her2 antibodies, or any antibodies, to the treatment of Her2 overexpressing cancer using a monoclonal antibody produced by hybridoma cell line ATCC No. HB 12078, or an antibody that binds to the same epitope.

12. Applicants argue that *in vivo* data is not required to enable the claimed invention and cite *In re Brana* to support their arguments (p. 9).

The argument has been considered but is not found persuasive because *In re Brana* does not enable the claimed invention nor teach the extrapolation of *in vitro* results to the enablement of an *in vivo* method for the reasons set forth above in the enablement rejection of section 5 with regards to *In re Brana*. Further, the *in vitro* model used in the specification is not recognized as correlating to the *in vivo* treatment of cancer and is not accepted as reasonably correlating for the reasons set forth above and in the enablement rejection of section 5 with regards to *in vitro* models.

13. Applicants argue that the observation made in Drexler's study of Hodgkin and Reed-Sternberg cell lines is not applicable to the cell lines used in the present application because they are not NCI panel cells and the NCI panel cells have been identified as valuable for the identification of anti-cancer therapeutic models. Applicants argue that the observation made by Drexler was not based on NCBI panel cells and the conclusion is not applicable (p. 10-11).

The argument has been considered but is not found persuasive because Drexler teaches a concept that does apply to the NCI panel cells. Drexler teaches the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the in-vivo cancer cells have been established and even for the bona fide cancer cell lines it is difficult to prove that the immortalized cells originated

from a specific cancer cell. As stated in the Office Action mailed 4/19/06, section 6, Applicants' *in vitro* studies to screen for antibodies that bind HER2 and induce apoptosis were conducted only in MCF7 and MDA-MB-435 cells (Example 6). SKBR3 cells were not used in the apoptosis screen and are not on the list of 60 human cancer cell lines used in the screen and maintained by the National Cancer Institute. The cell line MDA-MB-435, of the NCI panel has a disputed origin and studies provide convincing data that the cells are of melanoma origin instead of breast (see Cell Lines in the *In Vitro* Screen, p. 2, and "MDA-MB-435: Breast or Melanoma Origin?"). Clearly, Drexler's concepts apply to other *in vitro* cell lines as even the NCI panel line, MDA-MB-435, may not have originated from breast cells, hence verifying Drexler's teachings that "it is difficult to prove that the immortalized cells originated from a specific cancer cell" and "the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded". The NCI panel cells used in the *in vitro* screening of antibodies in the specification do not reasonably or predictably correlate to the *in vivo* treatment of cancer.

14. Applicants argue that Dermer discusses a single specific cell line that is not a NCI panel cell line, hence the Dermer teachings are not applicable (p. 12).

The argument has been considered but is not found persuasive because the concepts taught by Dermer are applicable to the NCI panel cell lines. As stated above in the enablement rejection of section 5: ""petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from

the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions." It is well-known in the art that cell lines must change physiologically to adapt to cell culture growth, hence they change and may lose or gain traits that are not representative of their *in vivo* counterparts. Further, it is well-known in the art that cell lines, in cell culture, do not duplicate nor represent the immunological, physiological, or biochemical environment of an *in vivo* system, hence the data obtained from an *in vitro* antibody screen would not be extrapolated to the *in vivo* treatment of cancer.

15. Applicants argue that Freshney teaches that "although the existence of such differences cannot be denied, it must be emphasized that many specialized functions are expressed in culture and as long as the limits of the model are appreciated, it can become a very valuable too". Applicants further state that Freshney teaches that "...cell culture systems have figured largely in the field of cancer chemotherapy, where the potential value of such systems for cytotoxicity

and viability testing is now widely accepted..." Applicants argue that Freshney supports the extrapolation of *in vitro* results to *in vivo* results (p. 13-14).

The argument has been considered but is not found persuasive because Freshney does not teach the extrapolation of *in vitro* results to *in vivo* results. The excerpts Applicants emphasized from Freshney teach that *in vitro* cell lines can be valuable tools for screening, that these tools have limits, and that they are accepted as tools for chemotherapeutic testing or screening. Freshney does not enable the *in vitro* extrapolation of an antibody screen to *in vivo* treatment of cancer.

16. **Conclusion:** No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura B. Goddard, Ph.D. whose telephone number is (571) 272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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